REMARKS

1. Preliminary Remarks

Claims 1 to 59 are currently pending. Claims 28 to 33 were rejected under 35 U.S.C. §102 as anticipated by Broder et al. U.S. Patent No. 5,968,972. Claim 28 has been amended herein. Additionally, claims 31 and 33 have been amended to clarify and correct a typographical error. Claims 1-27 and 34 to 59 are withdrawn from consideration as being drawn to a nonelected invention. Applicant reserves the right to pursue claims 1-27 and 34-59 in one or more divisional or continuation applications.

2. Rejection Of Claims 28 To 33 Under 35 U.S.C. §102

The Examiner rejected claims 28 to 33 under 35 U.S.C. §102 as being anticipated by Broder et al. U.S. Patent No. 5,968,972 ("Broder"). Applicant submits that Broder does not anticipate amended claim 28 or its dependent claims because (1) Broder does not suggest or teach that opioids such as naloxone, naltrexone, and nalmefene are inhibitors of P-glycoprotein; and (2) Broder also does not suggest or teach amounts of opioid inhibitors in the range of 0.0001 μm to 100 μm.

Broder teaches a method of increasing the bioavailability of antitumor agents (such as taxol) by administering a bioavailability-enhancing agent. Broder states that certain agents which apparently inhibit P-glycoprotein (PGP) drug transport activity, particularly cyclosporins, can be used to increase substantially oral bioavailability of poorly available or non-available pharmaceutical agents, for example, paclitaxel (formerly known as taxol) and etoposide. (Broder, column 3, lines 14-30). Broder's examples employ cyclosporine, a known PGP-inhibitor, and Broder's specification discusses cyclosporine at length. However, Broder states that the class of enhancing agents includes several other types of agents, including: "Agents active against endorphin receptors—morphine, morphine congeners, other opioids and opioid antagonists including (but not limited to) naloxone, naltrexone and nalmefene." (Broder, column 10, lines 28-31; *see also* column 9, line 44, to column 10, line 27 for Broder's list of enhancing agents).

The Examiner apparently concluded that Broder teaches that opioid antagonists such as naloxone, naltrexone and nalmefene are PGP-inhibitors, and therefore Broder

met Applicant's claim element requiring an opioid inhibitor of a ABC transporter protein. However, Broder does not suggest or teach that opioid antagonists such as naloxone, naltrexone and nalmefene are PGP-inhibitors. Although Broder states that PGP-inhibitors may be administered to increase oral availability, Broder also teaches that not all PGP-inhibitors are effective in this regard:

> Even this theoretical explanation does not account for our surprising discovery that certain P-glycoprotein inhibitors (e.g., cyclosporins and ketoconazole) increase oral bioavailability of specific target drugs to a high degree, whereas other agents known to be active P-glycoprotein inhibitors exhibit little activity as oral absorption enhancers for the same target drugs.

(Broder, column 9, lines 7-14 (emphasis added)). Further, Broder suggests that the bioavailability-enhancing agent may not have to be a PGP-inhibitor:

> We have observed in animal studies that certain multidrug resistance suppressing agents such as cyclosporine and ketoconazole, when administered orally together with and/or before drugs such as paclitaxel and etoposide, increase absorption of the latter drugs from the gut to an unexpected and surprising degree. It is not at all clear, however, that these observed results are due to the suppression of the P-glycoprotein pump.

(Broder, column 8, lines 50-57 (emphasis added)).

Since Broder does not disclose suggest or teach that opioids are PGP-inhibitors or ABC transfer protein inhibitors, it cannot anticipate a claim requiring an ABC transfer protein-inhibiting amount of an opioid.

Amended claims 28 and its dependent claims 29-33 relate to compositions comprising (a) an anti-tumor agent, wherein the anti-tumor agent is a substrate of an ABC drug transporter protein, and (b) an ABC drug transporter protein-inhibiting amount of an opioid inhibitor of an ABC drug transporter protein, wherein the amount is in the range of from 0.0001 μM to 100 μM. Applicant has discovered that opioid antagonists such as naloxone, naltrexone, and nalmefene are effective as inhibitors of ABC drug transporter proteins such as P-glycoprotein. Applicant disclosed the inhibition of PGP-mediated

transport of digoxin by naloxone, naltrexone, and nalmefene in Tables 1, 2 and 3, respectively of the present specification (pages 16-17 of the application).

Broder does not suggest or teach that opioid antagonists such as naloxone, naltrexone, and nalmefene are inhibitors of P-glycoprotein. Broder states very clearly that they are not sure whether PGP-inhibition is necessary or even relevant to their method:

> It is important to note that while we provide hypotheses as to the mechanisms of action which underlie our invention, we do not actually know the mechanism(s) responsible for the surprising findings discussed herein; and this does not impede one of skill in the art from practicing the invention described.

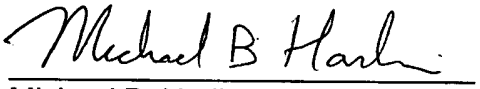
(Broder, column 9, lines 28-33). Again, Broder states that it is not necessary or even effective for the bioavailability-enhancing agent to be an inhibitor of PGP, since some agents that inhibit PGP were not effective as oral absorption enhancers as described and claimed by Broder. (See Broder, column 9, lines 7-14).

Furthermore, Broder also does not suggest or teach compositions comprising an amount in the range of 0.0001 μM to 100 μM of an opioid inhibitor of an ABC transfer protein. Applicant has disclosed this range in the specification at, for example, page 18, lines 17-19.

3. Conclusion

For the foregoing reasons, Applicant submits that the pending claims are not anticipated by Broder, U.S. Patent No. 5,968,972 and that the anticipation rejection may properly be withdrawn. Thus, claims 28-33 as amended herein are in condition for allowance. The Examiner is invited to telephone Applicant's representative to discuss any questions or be of any assistance to the Examiner in the reconsideration and allowance of this case.

Respectfully submitted,



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